REMARKS/ARGUMENTS

Upon entry of the instant amendment, claims 1-12 will be canceled without prejudice or disclaimer of the subject matter recited therein, and claims 13-41 will be added, whereby claims 13-41 will be pending. Claims 13, 19, 25, 27, 33 and 40 are independent claims.

To assist the Examiner's review of the newly-presented claims, Applicants note that the claims have been rewritten to be directed to the elected invention wherein R^1 is $-N(R^4)-W-R^5$.

Moreover, claims have been presented which are more in accordance with standard U.S. practice by including method claims as compared to use claims. For example, subject matter included in claims 9-12 is included in the presently submitted method claims 13-26 which have been modified with respect to the R^2 group in reciting that the C_1-C_8 alkyl group is unsubstituted, and is further defined in dependent claims as being linear.

Still further, pyrimidone derivative claims have been presented in different independent forms in independent claims 27, 33 and 40. Support for these variations, including variations in the recitations in the R^4 and R^5 groups, and the recitation of the R^2 group including C_1-C_8 alkyl group is unsubstituted and linear, and the R^3 group representing a 4-pyridyl group which may be substituted appear throughout the originally filed specification, including page 9 wherein the linear and branched, and substituted and unsubstituted alkyl groups and their substituents including C_6-C_{10} aryl group, such as phenyl group, 1-naphthyl group and 2-naphthyl group, are disclosed.

Still further, with respect to claims 38 and 40 attention is directed, for example, to the compounds disclosed in Table 2, such as compounds, 71, 79, 80, 84-86, 88, 89 and 91-93.

Still further, the specification has been amended to include explicit language for the presented claimed invention.

Reconsideration and allowance of the application are respectfully requested.

Response to Formal Matters

Applicants express appreciation for the acknowledgment of the claim of priority as well as receipt of the certified copy of the priority application.

Applicants also express appreciation for the return of the initialed Form PTO-1449, whereby the Examiner's consideration of Applicants' disclosure statement filed October 22, 2001 is of record.

Response To Maintaining of Lack Of Unity Of Invention

In response to the maintaining of the lack of unity of invention rejection, Applicants have canceled the non-elected subject matter of the non-elected species. Applicants' reserve their right to file one or more divisional and/or continuation applications to the non-elected subject matter.

Response To Rejection Under 35 U.S.C. 112, Second Paragraph

In response to the rejection of claim 9 under 35 U.S.C. 112, second paragraph, as being indefinite, Applicants respectfully submit the following.

In this ground of rejection, it is asserted that claim 9 is directed to the compound, and is therefore a substantial duplicate of claim 1. In response and as noted above, Applicants have amended the claims to be more in accordance with standard U.S. practice by presenting claims using standard U.S. method language as compared to use language. Accordingly, this ground of rejection is without appropriate basis and should be withdrawn.

Response To Rejection Under 35 U.S.C. 112, First Paragraph

Claims 10-12 are rejected under 35 U.S.C. § 112, first paragraph, as the Examiner asserts that the specification does not enable the claimed invention. In this ground of rejection, the Examiner is apparently asserting that the claims are not enabled for preventive treatment, and that the claims are not enabled for etiologies that are not related to "tau protein kinase I". Moreover, it appears that the rejection is questioning the ability to obtain therapeutic treatment of Down syndrome or "parkisonism".

In response, Applicants note that the "Background Art" section of the specification, and the articles cited therein establish that Applicants' invention is enabled for preventive treatment, is enabled for preventive treatment for the various recited diseases, and the therapeutic treatment of Down syndrome and "parkinsonism" is also enabled. In particular, as can be seen from a review of the information cited in the originally filed specification, one having ordinary skill in the art would be capable of practicing Applicants' disclosed and claimed invention without undue experimentation.

In particular, and as discussed in Applicants' specification, beginning on page 1, with respect to Alzheimer disease it has known that the degree of appearance of two characteristic pathological changes of Alzheimer disease correlates well to the degree of intellectual dysfunction. It is disclosed that it has been shown, referencing Biochem. Biophys. Res. Commun., 120, 855 (1984); EMBO J., 4, 2757 (1985); Proc. Natl. Acad. Sci. USA, 82, 4245 (1985), that senile plaques accumulate extracellularly, and amyloid βprotein has been elucidated as main components (abbreviated as "Aβ"). Moreover, it is disclosed that in the other pathological change, i.e., the neurofibrillary tangles, a double-helical filamentous substance called paired helical filament (abbreviated as "PHF") accumulate intracellularly, and tau protein, which is a kind of microtubule-associated protein specific for brain, has been revealed as its main component, referencing Proc. Natl. Acad. Sci. USA, 85, 4506 (1988); Neuron, 1, 827 (1988).

Moreover, it is disclosed that, on the basis of genetic investigations, presenilins 1 and 2 were found as causative genes of familial Alzheimer disease (Nature, 375, 754 (1995); Science, 269, 973 (1995); Nature. 376, 775 (1995)), and it has been revealed that presence of mutants of presenilins 1 and 2 promotes the secretion of Aβ, referring to Neuron, 17, 1005 (1996); Proc. Natl. Acad. Sci. USA, 94, 2025 (1997). It is disclosed that from these results, it is considered that, in Alzheimer disease, Aβ abnormally accumulates and agglomerates due to a certain reason, which engages with the formation of PHF to cause death of nerve cells. It is disclosed that it is expected that extracellular outflow of glutamic acid and activation of glutamate receptor responding to the outflow may possibly be important factors in an early process of the nerve cell

death caused by ischemic cerebrovascular accidents, referring to Sai-shin Igaku [Latest Medicine], 49, 1506 (1994).

Still further, it is disclosed that it has been reported that kainic acid treatment that stimulates the AMPA receptor, one of glutamate receptor, increases mRNA of the amyloid precursor protein (abbreviated as "APP") as a precursor of Aβ (Society for Neuroscience Abstracts, 17, 1445 (1991)), and also promotes metabolism of APP (The Journal of Neuroscience, 10, 2400 (1990)). Therefore, it is disclosed that it has been strongly suggested that the accumulation of Aβ is involved in cellular death due to ischemic cerebrovascular disorders. It is also disclosed that other diseases in which abnormal accumulation and agglomeration of Aβ are observed include, for example, Down syndrome, cerebral bleeding due to solitary cerebral amyloid angiopathy, Lewy body disease (Shin-kei Shinpo [Nerve Advance], 34, 343 (1990); Tanpaku-shitu Kaku-san Koso [Protein, Nucleic Acid, Enzyme], 41, 1476 (1996)) and the like. Furthermore, it is disclosed that as diseases showing neurofibrillary tangles due to the PHF accumulation, examples include progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, Guam parkinsonism-dementia complex, Lewy body disease and the like (Tanpakushitu Kakusan Koso [Protein, Nucleic Acid, Enzyme], 36, 2 (1991); Igaku no Ayumi [Progress of Medicine], 158, 511 (1991); Tanpakushitu Kakusan Koso [Protein, Nucleic Acid, Enzyme], 41, 1476 (1996)).

Still further, with respect to tau protein, it is disclosed that the tau protein is generally composed of a group of related proteins that forms several bands at molecular weights of 48-65 kDa in SDS-polyacrylamide gel electrophoresis, and it promotes the formation of microtubules.

It is disclosed that it has been verified that tau protein incorporated in the PHF in the brain suffering from Alzheimer disease is abnormally phosphorylated compared with usual tau protein (J. Biochem., 99, 1807 (1986); Proc. Natl. Acad. Sci. USA, 83, 4913 (1986)). Ii is also disclosed that an enzyme catalyzing the abnormal phosphorylation has been isolated. The protein was named as tau protein kinase 1 (abbreviated as "TPK1"), and its physicochemical properties have been elucidated (Seikagaku [Biochemistry], 64, 308 (1992); J. Biol. Chem., 267, 10897 (1992)). Moreover, cDNA of rat TPK1 was cloned from a rat cerebral cortex cDNA library based on a partial amino acid sequence of TPK1, and its nucleotide sequence was determined and an amino acid sequence was deduced (Japanese Patent Un-examined Publication [Kokai] No. 6-239893/1994). As a result, it has been revealed that the primary structure of the rat TPK1 corresponds to that of the enzyme known as rat GSK-3 β (glycogen synthase kinase 3β, FEBS Lett., 325, 167 (1993)).

It is further disclosed that it has been reported that Aβ, the main component of senile plaques, is neurotoxic (Science, 250, 279 (1990)). However, various theories have been proposed as for the reason why Aβ causes the cell death, and any authentic theory has not yet been established. Takashima et al. observed that the cell death was caused by Aβ treatment of fetal rat hippocampus primary culture system, and then found that the TPK1 activity was increased by Aβ treatment and the cell death by Aβ was inhibited by antisense of TPK1 (Proc. Natl. Acad. Sci. USA, 90, 7789 (1993); Japanese Patent Un-examined Publication [Kokai] No. 6-329551/1994).

In view of the foregoing, Applicants respectfully submit that their disclosure enables the use of compounds which inhibit the TPK1 activity to suppress the neurotoxicity of Aβ and the formation of PHF and inhibit the nerve cell death in the Alzheimer disease, thereby cease or defer the progress of the disease. Applicants also respectfully submit that the compounds are enabled to be used as a medicament for therapeutic treatment of ischemic cerebrovascular disorder, Down syndrome, cerebral amyloid angiopathy, cerebral bleeding due to Lewy body disease and the like by suppressing the cytotoxicity of Aβ. Furthermore, the compounds are enabled for use as a medicament for therapeutic treatment of neurodegenerative diseases such as progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, Guam parkinsonism-dementia complex, Lewy body disease, Pick's disease, corticobasal degeneration and frontotemporal dementia.

Applicants note that the rejection does not provide detailed remarks about the enablement and guidance provided in Applicants' originally filed disclosure, but instead points to the assertion that Alzheimer disease depletes acetylcholine, that Down syndome is related to the extra chromosome, and that "parkisonism" has been associated with dopamine. Whether or not these assertions are accurate, the question is not whether the diseases may have other characteristics than those discussed by Applicants. The question is whether Applicants have provided sufficient guidance so that one having ordinary skill in the art would be able to practice Applicants' invention without undue experimentation. Certainly, the answer to that question is in the affirmative, especially in view of the state of the art as discussed in Applicants' originally filed disclosure.

The rejection appears to support its assertion of non-enablement of the word "may" utilized in Applicants' specification. However, it is not one word that should be looked at in judging enablement, but the whole state of the art. Applicants respectfully submit that the state of the art as discussed in the originally filed application is enabling for Applicants' claimed invention. Therefore, if this ground of rejection is maintained, the rejection must be supported by technical reasoning with respect to the body of knowledge as disclosed by Applicants. In this regard, the Examiner is reminded that the burden is not on Applicants to establish that the claims are enabled, but is on the Examiner to support an enablement rejection using technical arguments. See, for example, "Training Materials for Examining Patent Applications with Respect to 35 U.S.C. Section 112, First Paragraph -- Enablement Chemical/Biotechnical Applications" and In re Marzocchi, 439 F.2d 220, 224, 169 USPQ 367, 369 (CCPA 1971).

In particular, it is noted that in Marzocchi, in reversing this rejection, the Court noted that the Patent Office should not be concerned with the breadth of the claims per se and that the burden of showing lack of enablement is on the Patent Office:

> Turning specifically to the objections noted by the board as indicated above, it appears that these comments indicated nothing more than a concern over the breadth of the disputed term . . . . The only relevant concern of the Patent Office under these circumstances should be over the truth of any such assertion.
>
> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of §112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. . . .
>
> [I]t is incumbent upon the Patent Office, whenever a rejection on this basis [lack of enablement] is made, to explain why it doubts the truth or accuracy of any

> statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.

Id. at 369-70 (emphasis in original). Therefore, the burden of showing lack of enablement is on the Patent and Trademark Office.

In view of the above, Applicants respectfully submit that the claims are enabled, and the enablement rejection should be withdrawn.

Response To Rejections Based Upon Prior Art

The claims are rejected based upon a number of documents. In particular, the following rejections appear in the Office Action:

(a) Claims 1, 2, 4-6 and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Skulnick et al., "Pyrimidinones. 1. 2-Amino-5-Halo-6-Aryl-4(3H)-Pyrimidinones. Interferon-Inducing Antiviral Agents", J. Med. Chem., Vol. 28, pp 1864-1869 (1985).

(b) Claims 1, 2, 4-6 and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Tani et al. (Not clear which document is being used.)

(c) Claims 1, 2, 4, 5 and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Stringfellow et al., U.S. Patent No. 4,619,933.

(d) Claims 1, 2, 4, 5 and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Fast et al., U.S. Patent No. 4,507,302.

(e) Claims 1 and 4-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Brana et al., Chemical Abstracts, 100:174768e,

(f) Claims 1-6 and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Tani et al., CA 84:44112b.

(g) Claims 1-6 and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Tani et al., JP 49-035631, JP 49-035633, JP 49-035634 and CAS printout.

(h) Claims 1, 4, 5 and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Ram, Chemical Abstract 116:59167.

(i) Claims 1, 4 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Buehler et al., CA 65:90645 and CAS printout.

(j) Claims 1, 4-6 and 8 are rejected under 35 U.S.C. 102(e) as being anticipated by Spohr et al., U.S. Patent No. 6,096,753.

(k) Claims 1, 4-6 and 8 are rejected under 35 U.S.C. 102(e) as being anticipated by Spohr et al., WO 98/24780 or WO 98/24782.

In response to these rejections, Applicants note that the claims as amended are not taught or suggested by the prior art of record.

In particular, Applicants note that none of the prior art of record teaches or suggests the methods, compounds and compositions as recited in Applicants' amended claims. For example, it does not appear that any of the documents utilized in the rejections teaches or suggests methods utilizing compositions as recited in Applicants' claims. Applicants note that WO 98/24782 does not

disclose Alzheimer disease in the specification; however, a review of the claims indicates that Alzheimer disease is included in claim 17.

However, the compounds disclosed as being included the invention of WO 98/24782 are indicated at, for example, page 23, beginning at line 17, to include R_{11} and R_{12} as each being independently an aryl or heteroaryl radical optionally substituted by 1-3 radical of the listed radicals. Accordingly, the compounds for treating diseases according to the invention of WO 98/24782 are disclosed as including such R_{11} and R_{12} groups.

Still further, the Table of compounds of interest disclosed in WO 98/24782 beginning at page 35, include R_{11} as being tert-butyl (at page 71) despite the fact that such compound is not included in the genus as disclosed by WO 98/24782. Therefore, this compound is not within the compounds disclosed by WO 98/24782 as being utilizable in his disclosed methods, and cannot be relied upon in connection with the treatment of diseases disclosed in WO 98/24782, let alone Alzheimer disease which is not even discussed in the specification.

Regarding the other documents of record, as noted above the claims have been amended, and it does not appear that any of these documents teaches or suggests the compounds and/or compositions presently recited by Applicants.

In view of the above, Applicants respectfully submit that the rejections are presently without appropriate basis and should be withdrawn.

P20810.A07

CONCLUSION

In view of the foregoing, the Examiner is respectfully requested to reconsider and withdraw the rejections of record, and allow all the pending claims.

Allowance of the application is requested, with an early mailing of the Notices of Allowance and Allowability.

If the Examiner has any questions or wishes to further discuss this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,
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